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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,066	10/19/2001	Michael Hallek	50125/019001	8894

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,066	HALLEK ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,29-32 and 35-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,29-32,35-40,42 and 43* is/are rejected.

7)☒ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 4/10/06. Claims 2-28, 33 and 34 have been cancelled. Claims 1, 30, 31, 35, 36 and 39-43 have been amended. Claims 1, 29-32 and 35-43 are pending in the application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Information Disclosure Statement

Information Disclosure Statements filed 2/6/06 and 4/27/06 have been identified and the documents considered. The signed and initialed PTO Form 1449s has been mailed with this action.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 29-32, 35-40 and 42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 121, 122, 130 and 143 of copending Application No. 10/498,163. **This rejection is maintained for reasons of record in the office action mailed 12/6/05 and restated below.**

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims 121, 122, 130 and 143 of U.S. application 10/498,163. That is, the cited claims of U.S. application 10/498,163 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, the instant claims and U.S. 10/498,163 claims recite a structural (cap or capsid) protein and the nucleic acid coding for the structural protein with an insertion after an amino acid such as 587 (amino acid N in SEQ ID NO:7 of the instant claims). Claim 121 of US application 10/498,691 specifically recites insertion of RGD, which is a ligand that interacts with cell surface integrin receptors and is specifically designed to increase infectivity to cells as recited in claim 1 of the instant invention. The specification of 10/498,163 teaches that the amino acid 587 recited in claim 122 is

specifically from AAV2 and corresponds to N of SEQ ID NO:7 of instant claim 1. The capsid proteins VP1, VP2 and VP3 are components of AAV particles and are all encoded by the same transcript and result from alternative splicing. Instant application 10/498,163 refers to the amino acids as numbered from the N-terminus of VP-1. However, the insertion if after amino acid 587 could be in VP-3 as recited in claim 29 and 30 of the instant invention as the amino acid recited as 587 is included in VP-1, VP2 and VP-3. An insertion of an RGD ligand at 587 alters binding at the heparan sulfate receptor as taught by 10/498,163.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the Application No. 10/498,163, then two different assignees would hold a patent to the claimed invention of Application No. 10/498,163, and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Argument

Applicants' request that the response to this rejection be deferred until allowable subject matter has been identified is acknowledged. However, the rejection is maintained until the recited claims are patented or a terminal disclaimer is filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 29-32, 35-40, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of structural proteins, which comprises at least one mutation, wherein the mutated structural protein comprises one or more amino acid insertion, which brings about an increase in infectivity of AAV. The amino acid insertions are located before and/or after at least one amino acid sequence found in SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8, wherein the mutated structural protein is capable of particle formation. **This rejection is maintained for reasons of record in the office action filed 10/16/03, 5/18/04, 6/29/05, 12/6/05 and restated below.**

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

The instant invention recites a structural protein of AAV2, which comprises at least one mutation wherein the mutated structural protein comprises one or more amino acid mutations that bring about an increase in infectivity. The structural protein is also capable of particle

formation. The amino acid insertion is directly adjacent to at least one amino acid in the sequences listed as SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. These sequences are found in AAV2 capsid proteins (see page 17, line 8-23). Furthermore, the claims are drawn to a nucleic acid coding for these structural protein as well as cells comprising the nucleic acid. As well, the claims are drawn to methods of preparing the structural proteins and use of the structural proteins to alter tropism of AAV2. The critical element of all of the claims is a structural protein comprising a mutation with one or more amino acid insertions.

The specification defines "structural proteins " as capsid proteins, which are VP1, VP2 and VP3 (see page 1, paragraph 2 and 3). These proteins are encoded by overlapping sequences of the same open reading frame leading to obligatory expression of all the capsid proteins (see page 2, line 1-10). The recited sequences within SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8 represent loop structures that were identified within the capsid proteins VP1, VP2 and VP3 of AAV2 (see page 11, line 10-18). These regions were identified by comparison of the crystal structure and nucleic acid sequences of three viruses CPV, AAV2 and B19. By insertions of amino acids within the loops, applicants endeavor to modify the capsid proteins such that they are more specific and efficient gene transfer vectors (see e.g. page 5, paragraph 3).

The potential mutations are large in number and diverse for the following reasons. By recitation of "amino acid insertion(s)", the insertion can be as small as a single amino acid or as large as a gene. Secondly, there can be multiple insertions within the structural protein, which leads to a complex and large number of possible structural proteins. For example, considering a single insertion prior to or after the recited amino acids, a collection of proteins would be generated totaling about 77. This collection would increase exponentially upon introduction of

multiple mutations within the singly mutated proteins. As guidance, applicants have only demonstrated insertion of a laminin P1 ligand into VP1 and VP3 (pages 16-20). Specifically, Tables 1 and 2 depict five insertion mutants in which laminin P1 ligand is inserted directly following R in SEQ ID NO:4 (ins447 or I-447), directly following FF in SEQ ID NO:5 (ins534 or I-534), directly following T in SEQ ID NO: 6 (ins573 or I-573), directly following N in SEQ ID NO:7 (ins587 or I-587) and directly following T in SEQ ID NO:8 (ins713 or I-713). One viral particle that results from insertion of P1 into amino acid 587 (I-587) is shown to have increased infectivity of M07-LP1-R and B16F10 cells. Therefore, of these insertions, only one can tolerate the mutation and form particles and have increased infectivity. This mutation is at site 587 (I-587). The specification also teaches at page 28 that VP3 protein was mutated by the insertion of Z34C domain of protein A but no indication about the ability of the structural protein to form particles or increase infectivity is provided. Post filing art by Reid et al (J. Virol. 76:4559-4566, 2002, referenced in applicants' arguments filed 11/22/04) demonstrate that this insertion is, like that in the instant specification, following amino acid 587 of VP3.

The disclosure of insertion of the P1 ligand at amino acid 587 of VP3 to alter specificity to the two cell types is not accompanied by a disclosure as to the relative properties of this structural protein or a correlation between the structure of this mutation and its ability to alter infectivity. Therefore, following the guidance in the specification only a single site of insertion has been identified and that is after amino acid 587 of AAV2 VP3. Hence, there is no clear description of the structural or functional characteristics required for any other mutated structural proteins to increase infectivity. Given the large number of mutant structural proteins envisioned by the invention and the inability to determine which mutant structural proteins will increase

infectivity and be capable of particle formation, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of a single species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus. Therefore, the skilled artisan cannot envision the detailed structure of the broad class of recited AAV mutant structural proteins regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that the protein is part of the invention and a reference to a potential method for isolating it. The disclosure of a single member of this genus does not suggest that the applicant was in possession of the genus.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 29-32, 35-40, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a structural protein of AAV2 which comprises a single amino acid insertion immediately following amino acid N in SEQ ID NO:7 (amino acid 587 of AAV2 VP3), does not reasonably provide enablement for any other structural protein of AAV2 which comprises amino acid insertion(s) is (are) directly adjacent to at least one amino acid in the sequences listed as SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record in the office action mailed 12/6/05 and restated below.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The instant claims are drawn to a structural protein of AAV2, which comprises at least one mutation wherein the mutated structural protein comprises one or more amino acid mutations that bring about an increase in infectivity. The structural protein is also capable of particle formation. As well, the claims are drawn to nucleic acids coding for the structural protein and cells comprising the nucleic acid, a process for preparation of the structural protein and methods for altering the tropism of AAV using the cell comprising nucleic acid encoding the structural protein. By insertions of amino acids within the loops, applicants endeavor to modify the capsid proteins such that they are more specific and efficient gene transfer vectors (see e.g. page 5, paragraph 3).

2) **Scope of the invention**. Specifically, the amino acid insertion(s) is (are) directly adjacent to at least one amino acid in the sequences listed as SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. The recited sequences within SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8 represent loop structures that were identified within the capsid proteins VP1, VP2 and VP3 by comparison of the crystal

structure as well as the nucleic acid sequences of three viruses CPV, AAV2 and B19 (see page 11, line 10-18). Given the broad range of points of insertion, the undefined nature of the requisite number of insertions and number of amino acids that comprise the insertion, the claims encompasses broad and diverse collection of structural proteins. The insertion is intended to be of amino acids that function to increase infectivity. For example, insertion of a ligand could decrease affinity of interaction with a native receptor and increase affinity to a non-native receptor. Hence, claim 31 recites that the structural protein has a change in "an' interaction of the structural protein with "a" cell membrane receptor. It would require undue experimentation to determine which of the structural proteins would result in an increase in infectivity of AAV that is capable of particle formation and can alter tropism of AAV2.

3) **Number of working examples and guidance**. VP1, VP2 and VP3 are encoded by overlapping sequences of the same open reading frame leading to obligatory expression of all the capsid proteins (see e.g. page 2, line 1-10). Following identification of "loop structures", applicants, as depicted in Tables 1 and 2, generate five insertion mutants in which laminin P1 ligand is inserted directly following R in SEQ ID NO:4 (I-447), directly following FF in SEQ ID NO:5 (I-534), directly following T in SEQ ID NO: 6 (I-573), directly following N in SEQ ID NO:7 (I-587) and directly following T in SEQ ID NO:8 (I-713). No further experiments were demonstrated with I-713 other than to determine its packaging efficiency. The specification teaches that two of the insertions I-447 and I-587 can form particles but the ability of I-534 and I-573 to form particles is two orders of magnitude less (table 2). P1 interacts with integrin receptor. To analyze the infectivity of the AAV2 particles resulting from the four mutations, B16F10 and RN22 cells expressing P1 specific integrin on their surface were infected with

particles produced comprising the mutant structural proteins. No binding of wild type AAV2 and I-534 and I-573 to these cells were detected. While, I-447 and I-587 were able to bind to both cells, B16F10 cells transfected with I-447 were as inefficient as wild-type cells in generating titer (table 3). Therefore, one viral particle that results from insertion of P1 into amino acid 587 (I-587) is shown to have increased infectivity of B16F10 cells. This mutant is at site 587 of AAV2 VP3. The specification also teaches at page 28 that VP3 protein was mutated by the insertion of Z34C domain of protein A but no indication about the ability of the structural protein to form particles or increase infectivity is provided. Post filing art by Reid et al (J. Virol. 76:4559-4566, 2002, referenced in applicants' arguments filed 11/22/04) demonstrate that this insertion is, like that in the instant specification, following amino acid 587 of VP3.

4) **State of Art**. AAV-2 can infect a wide variety of cell types according to Ruffing et al (page 3385, col 2, paragraph 2; applicant provided in the amendment filed 11/22/04) hence the vector has been considered a valuable tool for gene therapy for the delivery of therapeutic molecules. Mutational analysis of the AAV2 capsid proteins has been undertake to identify locations that will alter the tropism of AAV2 and hence "increase the infectivity". Despite numerous attempts to find locations that are tolerant of insertion and lead to an increase in infection, functionally relevant regions of AAV-2 did not always translate into actual sites for insertion. Buning et al (Gene Therapy, 2003, Vol 10, pages 1142-1151) review the art of targeting AAV-2 by insertion mutagenesis. According to Buning et al on page 1148, several parameters lead to the unpredictability of insertional mutagenesis (1) "surface display of a ligand alone is a prerequisite but not sufficient for a ligand-dependent infection by the virus mutant" (2) "scaffold sequences flanking the heterologous ligand are important for epitope display, (3) "Not

every ligand, even if comparable in length, is tolerated at a specific insertion site" (page 1148, col 1, (2)). Therefore, using surface locations as determination of sites for insertion of any amino acid is a highly unpredictable art. Accordingly, it is demonstrated by Buning et al that I-587 alone presents promise for receptor specific peptides (see page 1143, col 2, paragraph 2). Hence using the corresponding method of the instant invention, a single species of insertion sites has reproducibly been demonstrated.

Wu et al (JVI, 2000, Vol 74, pages 8635-8647, applicant provided in the amendment filed 11/22/04) undertook a more systemic approach to characterize the capsid protein. Wu et al teaches that the art of generating AAV2 structural proteins with mutations that exhibit increased infectivity and form particles with altered tropism is unpredictable. Wu generated 93 insertion mutants at 59 locations. Wu et al generated a functional map of the AAV2 capsid and demonstrated which sites could actually tolerate substitutions, deletions or insertions. The sites were mutated by insertion of epitopes or ligands, by alanine-scanning mutagenesis in which 2-5 amino acids are altered to alanine residues and epitope substitution mutations. In fact, Wu found that not all substitutions or insertions were the same and that regions that could tolerate alanine substitutions could not tolerate other types of substitutions and the ability to introduce FLAG into the capsid reduced or abolished particle formation (see Wu et al, page 8640, col 1-2 and table 4). Therefore, Wu et al inserted HA into loop structures, reasoning that insertion would not affect capsid assembly or stability. While 6 sites tolerated substitution, only two demonstrated altered tropism confirming that the state of the art of determining insertions sites based upon structural characteristics is highly unpredictable.

5) **Unpredictability of the art**. The instant specification suggests identifying surface located regions of the structural proteins by either comparison of sequences of several AAV serotypes or computer-assisted comparison of CPV, AAV2 and B19. Applicants then propose that utilization of these surface locations for insertional mutational would allow generation of particles that have an increase in infectivity. Applicants conclude "it is also possible likewise to introduce an insertion in to the five directly adjacent AAs located next to the bold AA, because these are likewise located within a loop in the AAV2 capsid" (page 16, line 25-28). However, applicants only demonstrate the operability of a single insertion site with a single type of amino acid insertion, a P1 ligand, that leads to increased infectivity of P1 receptor containing cells thus altering the tropism of this vector. Given the broad nature of the recited structural proteins and the unknown nature of the amino acid insertion and the unknown numbers of insertions, the invention has a high level of unpredictability. The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). As taught by Buning et al, it is highly unpredictable that demonstration of a surface loop will itself provide the functional characteristics for altered tropism or increased infectivity. Furthermore, the demonstration that P1 functions at I-587 to increase infectivity to B16F10 does not provide adequate teachings that any ligand in any site will also provide the recited functional characteristics. Finally, the ability to determine *a priori* the functional aspects of a protein based upon primary amino acid sequence

is poorly established in the art. For example, Tseng and Liang teach that protein surfaces in particle experience very different selective pressure than other functional domains and global protein sequence and structure similarity are often unreliable for function prediction (see Introduction). Smith and Zhang provide teachings that confirm that inconsistencies and outright errors are encountered when assigning probable function to sequences (see page 1222, col 2, paragraph 1).

6) **Summary**. The invention recites a structural protein of AAV2, which comprises at least one mutation wherein the mutated structural protein comprises one or more amino acid mutations that bring about an increase in infectivity. The structural protein is also capable of particle formation. Given the broad interpretation of before and after the recited sequences, the undefined nature of the requisite number of insertions and number of amino acids that comprise the insertion, the claims encompasses broad and diverse collection of structural proteins. It would require undue experimentation to determine which of the structural proteins would result in an increase in infectivity of AAV and is capable of particle formation with altered tropism.

In view of predictability of the art to which the invention pertains and the lack of guidance in the specification: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Arguments-35 USC § 112, 1st paragraph-written description and lack of enablement

To be completely responsive to the Office action mailed 11/2/05, applicants should have provided a specific response to the rejection under 35 USC 112, first paragraph for lack of written description. The amendment appears to be a bona fide attempt to respond completely to the office action mailed 12/6/05 as it appears that applicants intended that arguments directed against the rejection under 35 USC 112, first paragraph for lack of enablement are intended to be the same. (Under 35 USC § 1.135), " When a bona fide attempt to reply includes an omission that does not preclude action on the merits of the application (e.g., a reply fails to address a rejection or objection), the examiner may waive the deficiency in the reply and act on the application. The examiner may repeat and make final the rejection, objection, or requirement that was the subject of the omission." As such, the requirement is waived in attempts to expedite prosecution.

Applicants traverse the rejections under 35 U.S.C 112, first paragraph on pages 7-8 of the amendment filed 4/10/06. Applicants argue that the claims are now drawn to a structural protein from AAV2 that includes an insertion mutation positioned directly adjacent to one of 11 possible consecutive amino acid positions at 7 possible sites within the capsid protein. To this end, applicants argue that there is no evidence of record that would indicate that the specifically recited positions would not be workable or function with unpredictability. In fact, applicants argue that the evidence is that these sites are amenable to insertions suitable for retargeting as demonstrated in Wu et al and Shi and Bartlett.

Applicant's arguments filed 4/10/06 have been fully considered but they are not persuasive. Applicants have argued that several sites that could tolerate insertion have been demonstrated and there is no evidence that that the recited positions would not work. First, it is important to note that there is a functional requirement that the structural proteins that result from mutation must exhibit an increase in infectivity and also can form particles and have altered tropism. Applicants have only demonstrated a single structural protein comprising a P1 insertion that meets the functional requirements of increased infectivity, is capable of particle formation and altered tropism. The specification lacks any guidance as to the structural requirements of this structural protein that can provide increased infectivity, alter tropism or maintain particle formation. Therefore, the specification has failed to describe the genus of proteins that are recited. Furthermore, the art at the time of filing has demonstrated that it is highly unpredictable that by identification of loop structures, the ability to generate mutants that functional requirement that the structural proteins that result from mutation must exhibit an increase in infectivity and also can form particles and have altered tropism as set forth above. Specifically, Wu et al and Buning et al have demonstrated that many sites can tolerate insertions but only one in the case of Buning and two in the case of Wu et al could alter the tropism or increase infectivity. Several of the mutations tested by Wu et al overlap those recited here. Therefore, there is evidence in the art that the specific recited mutations do not provide a desired functional attribute. As a single insertion amongst the recited insertions result in a structural protein with the required attribute, the utility of the remaining insertions is also questionable. With regard to the post-filing reference of Shi et al, it is not clear from reading the reference that the inserts and methods described in the reference are taught explicitly in the instant specification. For example,

Shi et al appear to teach that an insertion following amino acid positions 584 and 588 cause an increase in infectivity but that the infectious nature and stability of the protein is the result of use of a linker attached to an RGD insertion that do not appear to be specifically taught in the specification. Any differences between the teachings of Shi et al and the instant specification must be considered as inventive experimentation considering the underdeveloped state and unpredictability of the art at the time of applicants' invention (see above). Therefore, Shi et al cannot be considered as providing evidence that applicants' claimed invention was enabled at the time of invention.

Conclusion

Claims 1, 29-32, 35-40, 42 and 43 are rejected.

Claim 41 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER